Transcranial direct current stimulation effects on auditory event-related potentials in Schizophrenia

A thesis submitted to the University of Newcastle, NSW, Australia for the degree of Doctor of Philosophy (Psychiatry)

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July 2014
STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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STATEMENT OF COLLABORATION

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

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Lilly Knechtel
ACKNOWLEDGEMENTS

This study was supported by the Schizophrenia Research Institute utilizing infrastructure funding from the New South Wales Ministry of Health and New South Wales Ministry of Trade and Investment (Australia). L. Knechtel was supported by a PhD scholarship of the Schizophrenia Research Institute and the University of Newcastle (Australia). The author is grateful for the assistance of her supervisors Ulrich Schall and Renate Thienel as well as Gavin Cooper for the technical support with EEG recordings, Ross Fullham for EEG data analysis advise and the organizational help from Vanessa Case. The author also thanks MRI specialist Peter Stanwell for assisting with magnetic resonance spectroscopy study design and Saadallah Ramadan and Todd Jolly for their support in MRS data analysis.
ABSTRACT

Transcranial direct current stimulation (tDCS) is considered a non-invasive and well-tolerated brain stimulation technique with very few adverse side effects. Importantly, tDCS does not directly evoke neuronal firing (as induced by electroconvulsive or transcranial magnetic stimulation), but instead alters the resting membrane potential of pre- and post-synaptic neurons dependent on the current polarity in the stimulated brain region. Animal studies suggest that changes in long-term potentiation occur via glutamate release in response to anodal tDCS, thereby affecting learning and memory. In clinical studies, a current not exceeding 2 mA/cm² is applied for 10–30 min via electrodes placed above the target brain region. To date, a number of clinical studies have reported some promising effects when treating patients with depression, chronic pain, schizophrenia, dementia, Parkinson’s disease and cerebral stroke. However, appropriately designed randomized controlled clinical trials are scarce and reported intervention effect sizes only vary from small to moderate, with little evidence for sustained long-term effects.

Particularly the effects of tDCS on human cognition are poorly understood, including the underlying neurophysiological mechanisms. Hence, the current thesis investigated the effects of anodal tDCS over the prefrontal cortex on auditory event-related potentials (ERPs) and related changes in the neurochemistry of the stimulated brain tissue with high-field proton magnetic resonance spectroscopy (MRS) in healthy volunteers.

The effects of a single session of 20 min of 2 mA left-prefrontal anodal versus sham stimulation on auditory ERPs was investigated by employing a randomized single-blind crossover design. Stimulation effects on cortical glutamate (Glu) and glutamine (Glx) levels were subsequently measured in a 3 Tesla MRS scan. tDCS
was associated with a significant increase of N1 amplitudes while smaller P3b amplitudes correlated with higher cortical Glu and Glx levels in the stimulated brain area when performing an auditory go/no-go discrimination task. tDCS did not change mismatch negativity, nor task performance or cortical Glu/Glx levels. Cortical Glu/Glx levels and N1 amplitudes were both depended on stimulation order (“sham” vs “active”).

Notwithstanding, increased N1 amplitudes with anodal tDCS support the notion of increased cortical excitability, thereby potentially supporting impaired cognitive processes in neuropsychiatric conditions. Hence, the effects of tDCS on ERPs were also investigated in schizophrenia. Schizophrenia patients usually present with significantly smaller N1, MMN and P3 amplitudes when compared to their healthy counterparts. This was also confirmed in the current study. However, anodal tDCS had no effect on any ERPs in schizophrenia patients and did not affect the performance in the go/no-go task. In fact, both groups, healthy controls and schizophrenia patients, performed equally well on this task.

Taken together, these findings indicate that a single application of tDCS increases cortical excitability in healthy subjects as indicated by larger N1 amplitudes but not in schizophrenia patients. However, it is important to emphasize that the current study only investigated the short term effects of a single tDCS application whereas therapeutic effects usually take place following repeated tDCS over several weeks. The repeated application of tDCS is more likely to induce changes in neuronal plasticity (e.g. via long-term potentiation), which in turn is thought to facilitate recovery and to support re-learning as well as other cognitive processes. Hence, tDCS may be a useful tool when combined with cognitive behaviour therapy. Carry-over effects from active to sham trials can potentially interfere with tDCS effects on cortical excitability and should be taken into account by future studies (e.g. by employing a between-subjects study design).
TABLE OF CONTENTS

STATEMENT OF ORIGINALITY ..................................................................................................... II
STATEMENT OF COLLABORATION ............................................................................................. II
ACKNOWLEDGEMENTS ................................................................................................................. III
ABSTRACT .......................................................................................................................................... IV
TABLE OF CONTENTS ..................................................................................................................... VI
INDEX OF FIGURES ...................................................................................................................... VIII
INDEX OF APPENDICES ................................................................................................................ IX
INTRODUCTORY LIST OF ABBREVIATIONS ............................................................................ XI

1. TRANSCRANIAL DIRECT CURRENT STIMULATION: NEUROPHYSIOLOGY AND CLINICAL APPLICATIONS ............................................................................................................ 12
   1.1. TRANSCRANIAL BRAIN STIMULATION ..................................................................................... 12
   1.2. HOW DOES TDCS WORK? .......................................................................................................... 2
   1.3. ADVERSE SIDE EFFECTS OF TDCS ............................................................................................. 5
   1.4. CLINICAL APPLICATIONS OF TDCS ............................................................................................ 6
       1.4.1. DEPRESSION ........................................................................................................................................... 7
       1.4.2. PAIN ......................................................................................................................................................... 9
       1.4.3. CEREBRAL STROKE .............................................................................................................................11
       1.4.4. NEURODEGENERATIVE & NEURODEVELOPMENTAL BRAIN DISORDERS .....................................12
   1.5. CONCLUSION ............................................................................................................................. 14

2. TRANSCRANIAL DIRECT CURRENT STIMULATION OF PREFRONTAL CORTEX: AN AUDITORY EVENT-RELATED POTENTIAL AND PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY ................................................................................................................ 15
   2.1. INTRODUCTION ........................................................................................................................ 15
   2.2. MATERIALS AND METHODS ..................................................................................................... 18
       2.2.1. SUBJECTS ..............................................................................................................................................18
       2.2.2. STUDY DESIGN AND TDCS PROCEDURE ...........................................................................................19
       2.2.3. STIMULI, EEG RECORDING, AND ERP EXTRACTION .......................................................................20
       2.2.4. MRS ACQUISITION ..............................................................................................................................22
       2.2.5. STATISTICAL ANALYSES ......................................................................................................................24
   2.3. RESULTS .................................................................................................................................... 25
       2.3.1. BEHAVIOURAL DATA ..........................................................................................................................25
       2.3.2. ERP DATA .............................................................................................................................................25
       2.3.3. MRS DATA ............................................................................................................................................26
   2.4. DISCUSSION ................................................................................................................................ 27
3. TRANSCRANIAL DIRECT CURRENT STIMULATION OF PREFRONTAL CORTEX: AN AUDITORY EVENT-RELATED POTENTIAL STUDY IN SCHIZOPHRENIA ..........29

3.1. INTRODUCTION ...........................................................................................................................................29
3.2. METHODS ..........................................................................................................................................................31
  3.2.1. SUBJECTS ................................................................................................................................................31
  3.2.2. TDCS PROCEDURE AND STUDY DESIGN ............................................................................................32
  3.2.3. EEG RECORDING AND ANALYSES ........................................................................................................32

3.3. RESULTS .........................................................................................................................................................32
  3.3.1. DEMOGRAPHIC AND CLINICAL DATA .................................................................................................32
  3.3.2. BEHAVIOURAL DATA .............................................................................................................................33
  3.3.3. ERP DATA .............................................................................................................................................33

3.4. DISCUSSION ....................................................................................................................................................35

4. PROJECT SUMMARY, LIMITATIONS AND CONCLUSION ..............................................................................38

LIST OF ABBRIVIATIONS FOR APPENDIX ........................................................................................................43

APPENDICES .........................................................................................................................................................45

BIBLIOGRAPHY ......................................................................................................................................................67
INDEX OF FIGURES

FIGURE 1: PubMed identified 1146 publications when using the search phrase 'transcranial direct current stimulation'. Publications per annum are given between 2000 and December 2013. .................................................................................. 6

FIGURE 2: Left-dorsolateral prefrontal voxel position for the acquisition of the spectroscopic data ................................................................................................................23

FIGURE 3: N1 auditory ERPs (grand averages recorded at Fz) in response to standard stimuli in the duration-deviant condition (passive listening task) significantly increase with tDCS (p<0.02). Arrow marks stimulus onset; negative polarity is upwards. ...........................................................................................26

FIGURE 4: Event-related potentials (ERPs; negative up) recorded whilst performing an auditory go/no-go discrimination task (A) or a passive auditory listening task (B & C). Patient ERPs are presented as thick lines whereas healthy subject data are presented as thin lines. Grey represents “sham” stimulation and black tDCS data. Arrow marks stimulus onset. (A) P3b amplitudes at Pz in response to target stimuli and (B) Mismatch Negativity (MMN) at Fz in response to duration deviants were significantly smaller in patients. (C) N1 amplitudes at Fz significantly increased with tDCS in healthy subjects only ...........................................................................................................................34
# INDEX OF APPENDICES

**Table 1**: Demographics and tDCS Order for Healthy Control Group .................45

**Table 2**: ERPs of Healthy Control Group after Sham tDCS - MMN and P3a ..........46

**Table 3**: ERPs of Healthy Control Group after Sham tDCS - N1 and P3b ..........47

**Table 4**: ERPs of Healthy Control Group after Active tDCS - MMN and P3a .......47

**Table 5**: ERPs of Healthy Control Group after Active tDCS – N1 and P3b .........48

**Table 6**: Demographics and tDCS Order of Schizophrenia Patients ..................49

**Table 7**: ERPs of Schizophrenia Patients after Sham tDCS – MMN and P3 ..........50

**Table 8**: ERPs of Schizophrenia Patients after Sham tDCS – N1 ....................51

**Table 9**: ERPs of Schizophrenia Patients after Active tDCS – MMN and P3 .....52

**Table 10**: ERPs of Schizophrenia Patients after Active tDCS – N1 ..................53

**Table 11**: ERP Mean Data for Both Groups for Sham and Active tDCS ..............55

**Table 12**: Behavioural Data for Both Groups .................................................56

**Table 13.1**: Metabolites measured by MRS in Healthy Control Group after Sham tDCS – Glu, Gln ..........................................................57

**Table 13.2**: Metabolites measured by MRS in Healthy Control Group after Sham tDCS – GABA, Asp and NAA ........................................58

**Table 13.3**: Metabolites measured by MRS in Healthy Control Group after Sham tDCS – NAAG, Ala and Glc ........................................59

**Table 13.4**: Metabolites measured by MRS in Healthy Control Group after Sham tDCS – Cr, PCR and GPC .........................................60

**Table 13.5**: Metabolites measured by MRS in Healthy Control Group after Sham tDCS – Ins and Lac ..............................................61
<table>
<thead>
<tr>
<th>Table Number</th>
<th>Table Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1</td>
<td>Metabolites measured by MRS in Healthy Control Group after active tDCS – Glu, Gln</td>
</tr>
<tr>
<td>14.2</td>
<td>Metabolites measured by MRS in Healthy Control Group after active tDCS – GABA, ASP and NAA</td>
</tr>
<tr>
<td>14.3</td>
<td>Metabolites measured by MRS in Healthy Control Group after active tDCS – NAAG, ALA and GLC</td>
</tr>
<tr>
<td>14.4</td>
<td>Metabolites measured by MRS in Healthy Control Group after active tDCS – Cr, PCR and GPC</td>
</tr>
<tr>
<td>14.5</td>
<td>Metabolites measured by MRS in Healthy Control Group after active tDCS – Ins and Lac</td>
</tr>
</tbody>
</table>
INTRODUCTORY LIST OF ABBREVIATIONS

EEG = Electroencephalography
ERP = Event-related Potential
Glu = Glutamate
Glx = Glutamate and Glutamine
MMN = Mismatch Negativity
MRS = Magnetic Resonance Spectroscopy
SAPS = Scale for the Assessment of Positive Symptoms
SANS = Scale for the Assessment of Negative Symptoms
tDCS = Transcranial Direct Current Stimulation